Available online on 15.05.2017 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open access to Pharmaceutical and Medical research

Review Article

ILOPERIDONE: NEWER ATYPICAL ANTIPSYCHOTIC FOR SCHIZOPHRENIA

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Article Info: Received 31 March 2017; Review Completed 12 April 2017; Accepted 12 April 2017, Available online 15 May 2017

Cite this article as:

Dutta SB, Beg MA, Kaur A, Vishal S, Iloperidone: Newer Atypical Antipsychotic for Schizophrenia, Journal of Drug Delivery and Therapeutics. 2017; 7(3):8-10

DOI: http://dx.doi.org/10.22270/jddt.v7i3.1441

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ABSTRACT

The optimal treatment of schizophrenia poses a challenge to develop more effective treatments and safer drugs, to overcome poor compliance, discontinuation and frequent switching with available antipsychotics. Many antipsychotic medications are currently approved by FDA for the treatment of schizophrenia, but response to these agents remains highly variable. Iloperidone is a new dopamine type 2/serotonin type 2A (D_2/5-HT_{2A}) antagonist structurally related to risperidone, expected to give better efficacy with less extrapyramidal symptoms than D_2 receptor antagonist antipsychotics. Iloperidone is more efficacious in terms of cognitive functions, less problematic regarding weight gain and metabolic disturbances.

Keywords: iloperidone, pharmacology, pharmacokinetics, efficacy, safety

INTRODUCTION

Schizophrenia is severely debilitating psychiatric disorder observed worldwide, causing recurring and progressive episodes of positive and negative symptoms, and disturbed cognitive function. The optimal treatment of schizophrenia poses a challenge to develop more effective treatments and safer drugs, to overcome poor compliance, discontinuation and frequent switching with available antipsychotics. Many antipsychotic medications are currently approved by FDA for the treatment of schizophrenia, but response to these agents remains highly variable. Atypical antipsychotics are considered as the choice of treatment of schizophrenia as they lack extrapyramidal side effects (EPSE) and lack of sustained prolactin elevation[1]. Considering all exposed, iloperidone has showed a good overall effectiveness profile despite dosing (12-24mg/day) against placebo and haloperidol [2, 3].

Iloperidone newer 2nd generation antipsychotic approved in 2009 found to be equally efficacious to haloperidol, risperidone and Olanzapine. Iloperidone is more efficacious in terms of cognitive functions, less problematic regarding weight gain and metabolic disturbances. Iloperidone is the 1st antipsychotic with specific genetic markers. Six single nucleotide polymorphisms identified that correlate with iloperidone response [4].

MECHANISM OF ACTION

Iloperidone a piperinidyl benzisoxazole derivative structurally related to risperidone. Iloperidone is a novel 2nd generation antipsychotic and like risperidone, ziprasidone and other atypical antipsychotics, iloperidone has high affinity for 5HT2A, D2 and D3 receptors and has moderate affinity for D4, 5HT6, 5HT7 and alpha-1receptors.Iloperidone has low affinity for 5HT1A, 5HT2C, D1, H1 receptors and has no

appreciable affinity for muscarinic M1-M5 receptors. Iloperidone's receptor affinity profile regarding 5HT2 and D2 resembles other 2nd generation antipsychotics and would predict its efficacy as an antipsychotic in general, and lowered likelihood to be associated with extrapyramidal symptoms [1, 5-8]. Affinity for the 5HT1A/6 could potentially enhance cognition and 5HT2C may enhance iloperidone's efficacy in treating the negative symptoms and may also provide the anxiolytic effect. Affinity for 5HT6 could improve the cognitive function [1, 6].

PHARMACOKINETICS

Iloperidone is rapidly absorbed reaching peak concentration between 2 and 5 hours after oral administration with a bioavailability of 96% [9-11]. Food did not alter the bioavailability. The plasma half-life of iloperidone varies between 5.4–7 hours and significantly delayed to 33.7 hours in patients with renal impairment [12]. Plasma protein binding is 93%. Volume of distribution of the drug is large [11]. Elimination of iloperidone is mainly through hepatic, metabolism to O-desmethyl iloperidone and 2-hydroxyl iloperidone by CYP2D6 and CYP3A4. Subsequent changes of these metabolites occur via oxidation and conjugation with glucoronic acid. Biliary excretion appears to be the predominant elimination pathway, iloperidone is highly metabolized, <1% of the drug excreted unchanged [1, 6].

Dose:

Dose initiated with 1mg BD and maintenance dose is 12mg/day (6mg BD). The maximum dose can be kept upto 24mg/day (12mg BD). The serum levels of iloperidone that corresponds with maximum therapeutic response were 5 -8 ng/ml [1].

Adverse drug reactions:

Safety data obtained from the pooled four week and six week, fixed dose or flexible dose phase 2 and 3 studies[13-15]. The drug side effects like orthostatic hypotension, dry mouth, dyspepsia, weight gain, QTc prolongation, and somnolence have been reported during the trials.The side effects as dizziness, tachycardia and weight gain at least twice as common with higher doses (20-24mg/day) than with lower doses (10-16mg/day) [9]. Insomnia and anxiety have been observed in long term studies comparing iloperidone with haloperidol [14].

Drug interactions:

The importance of CYP2D6 in iloperidone clearance is underlined by its interaction with potent inhibitors of this enzyme. A dosage reduction of the drug needed if administered with enzyme inhibitors as fluoxetine, erythromycin, azole antifungals and protease inhibitors, as the drug is metabolized by CYP3A4 and CYP2D6.

Use in special circumstances [9, 15-16]

Safe use of iloperidone during pregnancy is not established. FDA leveled the drug as category C for pregnancy risk. Safety of the drug during lactation is also not established.

Advantages:

Prolactin levels are not significantly affected by the drug. Iloperidone is considered to be a prolactin sparing atypical antipsychotic, iloperidone induced hyper-prolactinemia may rarely be encountered as a side effect in susceptible individuals [17]. The favourable Extrapyramidal side effects (EPSE) and akathesia profile of iloperidone makes it an attractive choice for patients whose compliance is limited by these side effects [18]. Switching to iloperidone from discontinuation of previous antipsychotics has revealed results in consistency with previous studies regarding favorable akathesia and EPSE profile [19].

Flexible dosing of iloperidone for maintenance phase therapy with a modal dose of 12mg/day was effective in preventing relapse in subjects[20].

Use:

As a broad spectrum antipsychotic with efficacy against positive &negative symptoms and particularly improves cognitive symptoms, makes it a promising agent in acute schizophrenia. It has excellent tolerability profile.

SUMMARY

Schizophrenia is a severely debilitating psychiatric disorder worldwide, with a median life time prevalence of 0.7-1%. Optimal treatment of the disease is still challenging to develop safe and effective antipsychotic drugs. Iloperidone is a novel 2nd generation antipsychotic drug for the treatment of schizophrenia. As it has a low risk of causing the extrapyramidal symptoms and adverse metabolic effects. However many disadvantages like orthostatic hypotension, risk of QT prolongation must be kept in mind. To conclude it may be a very useful and safe option for the treatment of schizophrenia but it doesn't necessarily possess any distinct advantage over other antipsychotic agents.

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